Summary of Evidence

When to start ART in infants

Martina Penazzato
ATC HIV/AIDS Department
WHO Geneva
Search Strategy

- Medline
- Embase
- BMJ Clinical Evidence
- The Cochrane Library
- Trip Database
- SUM search
- Bandolier
- Institute for Clinical Systems Improvement
- CROI 2005-2008 Abstract book

Pediatric or Children or Infants
HIV infection
Antiretroviral treatment
Highly active antiretroviral therapy
Drug name

Found: 453 clinical trials, 9 meta-analysis, 152 RCT, 328 review, 257 multicenter studies
Of interest: 70
Studies- Inclusion Criteria

- ✓ Infant subjects
- ✓ Infants well represented
- ✓ Outcomes stratified according to age
- ✓ Early antiretroviral treatment
- ✓ Early vs deferred
References selected

- **Pediatric European Network for Treatment of AIDS (PENTA)**. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. AIDS. 2004; 18:237-245. Updated 5 years outcomes, CROI 2008
- **European Infant Collaboration group**. Effect of early antiretroviral therapy on the risk of AIDS/death in HIV infected infants: the European Infant Collaborative Study. (Submitted)
- **Prendergast A**, Mphantswe W, Tudor-Williams G et al. Early immunological suppression with three-class antiretroviral therapy in HIV-infected African infants. (Submitted)
### When to start treatment in Infants

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Relative importance (rank 1→9 most critical)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (1st year)</td>
<td>9</td>
<td>critical</td>
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<tr>
<td>Mortality (5 years)</td>
<td>9</td>
<td>critical</td>
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<tr>
<td>Disease progression (clinical definition)</td>
<td>8</td>
<td>critical</td>
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<tr>
<td>Severe/LT events</td>
<td>7</td>
<td>critical</td>
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<tr>
<td>Major Adverse Events</td>
<td>7</td>
<td>critical</td>
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<tr>
<td>Detectable viral load</td>
<td>6</td>
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<td>CD4</td>
<td>6</td>
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<td>WAZ/HAZ</td>
<td>6</td>
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<tr>
<td>Drug resistance</td>
<td>5</td>
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<tr>
<td>Switch rate</td>
<td>5</td>
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<tr>
<td>Default rate</td>
<td>5</td>
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</table>
### Ranking the evidence...

<table>
<thead>
<tr>
<th>Comparison:</th>
<th>EARLY vs DEFERRED ANTIRETROVIRAL TREATMENT IN INFANTS (≤ 11 MONTHS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome:</td>
<td>EARLY MORTALITY (&lt;1&lt;sup&gt;ST&lt;/sup&gt; YEAR)</td>
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<tr>
<td>Population group:</td>
<td>HIV INFECTED INFANTS (≤ 11 MONTHS)</td>
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<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Directness or generalisability</th>
<th>Imprecise or sparse data</th>
<th>Other factors</th>
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Design

- 2 RCT
  - CHER study
  - Prendergast et al.

- 11 “Observational”
  - 4 trials
  - 6 cohort studies
  - 1 case control study

Only 3 studies in RLS
Limitations

- Was concealment of allocation to treatment group adequate?
- Were the participants and investigators blinded?
- Was an ITT analysis reported?
- Were all the withdrawals and patients lost to follow up accounted for?
- Was the trial stopped early for benefit?

Prendergast study not blinded:
MINOR LIMITATION
NO DOWNGRADE! +4
Consistency

Consistency refers to the similarity of estimates of effect across studies.

To evaluate the degree of consistency of the results of the available studies you should evaluate the direction and size of the effect.

IMPORTANT INCONSISTENCY
DOWN GRADE -1!
Indirectness

✓ Indirect comparison?
✓ Indirect population?

1. Different inclusion criteria between the two studies.
2. 80% were not breastfed in CHER and 60% in P. study. How is it going to be in breastfeeding population?

INDIRECT POPULATION
SOME UNCERTAINTY
DOWNGRADE! -1 +2
Imprecision

- Sample size: Prendergast study small sample size apparently enough powered
- Number of events: $<300$
- Confidence interval: 95% CI

IMPRECISE DATA
DOWNGRADE! -1  +1
Other Factors

- Publication/reporting bias
- Large effects
- Dose response curve
- Direction of confounding factors

CHER study was discontinued because of benefits HR 0.24 (95%CI)

Prendergast study inclusion criteria are likely to reduce the effect (reduction in mortality)

UPGRADE!!
+1 plus +1 ➔ +3
The majority of the observational studies available were not designed to compare "early initiation" vs "clinical-immunological guided initiation" therefore what follows is mainly an inference from observational studies that assess early treatment outcomes OR clinical-immunological guided initiation outcomes.

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<tr>
<td>9</td>
<td>Observational</td>
<td>All but one were not designed to assess &quot;Early-vs-Deferred&quot;</td>
<td>Direction and size of the effect appear consistent (all but Malawi)</td>
<td>Early immunological or clinical guided is not as early in asymptomatic children: Indirect comparison RLS vs RuLS (very different mortality background as well as different breastfeeding approach): Indirect population Major uncertainty</td>
<td>Good sample sizes</td>
<td>The confounder is likely to increase the outcome</td>
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<tr>
<td>2</td>
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Ranking

Software
GRADEprofiler 3.2 beta
Final Ranking

Starting ART treatment in all infants ≤ 11 months compared with waiting for clinical or immunological eligibility is supported by a LOW TO VERY LOW QUALITY OF EVIDENCE.
Thank you!

“When a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve” - Karl Popper